

CLAIMS

1. A method for treating a living animal body afflicted with disorders which may be treated by double inhibition of serotonin (5-HT) and noradrenaline (NA) reuptake while limiting the risk of cardiovascular disturbances, comprising the step of administering to the living animal body a mixture of enantiomers of milnacipran (Z(±)-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide) and/or of at least one of its metabolites, as well as their pharmaceutically-acceptable salts, such mixture being enriched in the (1S,2R) enantiomer, which administration is effective for alleviation of such disorder.
- 10 2. A method of claim 1, wherein the cardiovascular disturbances correspond to an increase in blood pressure and/or an increase in heart rate.
3. A method of claim 2, wherein the increase in blood pressure corresponds to an increase in diastolic blood pressure.
- 15 4. A method of claim 1, which also limits the risks of organ and/or tissue toxicity.
5. A method of claim 4, wherein the organ toxicity is cardiac toxicity and the tissue toxicity is hepatic and/or renal toxicity.
- 20 6. A method of claim 1, wherein the (1S,2R) enantiomer of milnacipran is the hydrochloride of Z-(1S,2R)-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide (F2695).
7. A method of claim 1, wherein the metabolite is selected from:
  - o the hydrochloride of Z-phenyl-1-aminomethyl-2-cyclopropanecarboxylic acid (F1567),
  - o phenyl-3 methylene-3-4-pyrrolidone-3 (F1612),
  - 25 o the hydrochloride of Z-(para-hydroxyphenyl)-1-diethylaminocarbonyl-1-aminomethyl-2-cyclopropane (F2782),
  - o the oxalic acid of Z-phenyl-1-ethylaminocarbonyl-1-aminomethyl-2-cyclopropane (F2800), and
  - o the hydrochloride of Z-phenyl-1-aminocarbonyl-1-aminomethyl-2-cyclopropane (F2941).
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8. A method of claim 7, wherein the metabolite is the hydrochloride of Z-(para-hydroxyphenyl)-1-diethylaminocarbonyl-1-aminomethyl-2-cyclopropane (F2782).
9. A method of claim 1, wherein the mass/mass ratio between the (1S,2R) enantiomer and the (1R,2S) enantiomer in the mixture is greater than 95:5 ((1S,2R):(1R,2S)).
10. A method of claim 1, wherein the mass/mass ratio between the (1S,2R) enantiomer and the (1R,2S) enantiomer in the mixture is greater than 99:1 ((1S,2R):(1R,2S)).
11. A method of claim 1, wherein the mass/mass ratio between the (1S,2R) enantiomer and the (1R,2S) enantiomer in the mixture is greater than 99.5:0.5 ((1S,2R):(1R,2S)).
12. A method of claim 1, wherein the mixture of enantiomers is substantially pure in the hydrochloride of Z-(1S,2R)-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide (F2695).
13. A method of claim 1, wherein the mixture of enantiomers is substantially pure in the hydrochloride of Z-(para-hydroxyphenyl)-1-diethylaminocarbonyl-1-aminomethyl-2-cyclopropane (F2782).
14. A method of claim 1, wherein the drug is intended to treat or to prevent a disorder or condition selected from depression, in particular deep depression, resistant depression, depression in the elderly, psychotic depression, depression induced by treatment with interferon, depressive state, manic-depressive syndrome, seasonal depressive episodes, depressive episodes related to general health status, depressive episodes related to mood-altering substances, bipolar disease, schizophrenia, generalized anxiety, morose and marasmic states, stress-related diseases, panic attacks, phobias, in particular agoraphobia, obsessive-compulsive disorders, behavioral disorders, oppositional disorders, post-traumatic stress disorder, depression of the immune system, fatigue and accompanying pain syndromes, chronic fatigue syndrome, fibromyalgia, and other functional somatic disorders, autism, disorders characterized by attention deficit due to general health status, attention disorders due to hyperactivity,

5 eating disorders, neurotic bulimia, neurotic anorexia, obesity, psychotic disorders, apathy, migraine, pain and in particular chronic pain, irritable bowel syndrome, cardiovascular diseases and in particular anxiety-depressive syndrome in myocardial infarctus or in hypertension, neurodegenerative diseases and related anxiety-depressive syndromes (Alzheimer's disease, Huntington's chorea, Parkinson's disease), urinary incontinence, in particular urinary incontinence related to stress and enuresis, drug addition and in particular anxiety-addiction to tobacco, in particular to nicotine, to alcohol, to narcotics, to drugs, to analgesics used in weaning-off from these addictive states.

10 15. A method of claim 14, wherein the disorder is selected from depression, in particular deep depression, resistant depression, depression in the elderly, psychotic depression, depression induced by treatments with interferon, depressive state, manic-depressive syndrome, seasonal depressive episodes, depressive episodes related to general healthy status, depression related to mood-altering substances.

15 16. A method of claim 14, wherein the disorder is selected from fatigue and the associated pain syndromes, chronic fatigue syndrome, fibromyalgia, and other functional somatic disorders.

20 17. A method of claim 14, wherein the disorder is selected from urinary incontinence, in particular urinary incontinence related to stress and enuresis.

18. A method of claim 14, wherein the condition is selected from drug addiction, including anxiety-addiction to tobacco, nicotine, alcohol, narcotics, drugs, and/or analgesics used in weaning-off from these addictive states.

25 19. A method of claim 1, wherein patients may be defined as children, the elderly, patients with hepatic and/or renal insufficiency, patients receiving treatment that induces hepatic or renal organ and/or tissue toxicity, patients receiving treatment for a heart condition, patients receiving treatment that induces cardiovascular side-effects, patients having a history of cardiovascular disease and/or suffering from cardiovascular disorders.

30 20. A method of claim 19, wherein the history of cardiovascular disease and/or cardiovascular disorders is chosen among myocardial infarctus, cardiac rhythm

disorders (tachycardia, bradycardia, palpitations), blood pressure disorders (hypo- or hypertensive patients) and heart disease.

21. A method of claim 1, wherein the drug comprises:

5           a) the mixture of enantiomers enriched in the (1S,2R) enantiomer of milnacipran and/or of at least one of its metabolites as well as their pharmaceutically-acceptable salts, and

          b) at least one active compound selected from the psychotropics, in particular antidepressants, and antimuscarinic agents,

10           as associated products for use simultaneously, separately or staggered in time for the treatment or the prevention of depression, in particular deep depression, resistant depression, depression in the elderly, psychotic depression, depression induced by treatment with interferon, depressive state, manic-depressive syndrome, seasonal depressive episodes, depressive episodes related to general health status, depressive episodes related to mood-altering substances.

15   22. A method of claim 1, wherein the drug comprises:

          a) the mixture of enantiomers enriched in the (1S,2R) enantiomer of milnacipran and/or of at least one of its metabolites as well as their pharmaceutically-acceptable salts, and

20           b) at least one other active substance selected among the active compounds that induce organ toxicity and the active compounds that induce cell toxicity, in particular hepatic and/or renal,

          as associated products for use simultaneously, separately or staggered in time for the treatment or the prevention of conditions or disorders that can be managed by double inhibition of serotonin (5-HT) and noradrenaline (NA) reuptake.

25   23. A method of claim 1, wherein the drug comprises:

          a) the mixture of enantiomers enriched in the (1S,2R) enantiomer of milnacipran and/or of at least one of its metabolites as well as their pharmaceutically-acceptable salts, and

30           b) at least one other active substance selected among the active compounds that induce cardiovascular side effects,

as associated products for use simultaneously, separately or staggered in time for the treatment or the prevention of conditions or disorders that can be managed by double inhibition of serotonin (5-HT) and noradrenaline (NA) reuptake.